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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/816,099	03/31/2004	Katalin Varadi	P-279.00	9454

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EXAMINER	
KOSSON, ROSANNE	
ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
11/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/816,099	VARADI ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 and 11 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-13 and 22-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-13 and 22-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendments filed on November 6 and 11, 2008 have been received and entered. Claim 1 has been amended. No claims have been canceled. Claim 24 has been added. Claims 9 and 14-21 were previously canceled. Accordingly, claims 1-8, 10-13 and 22-24 are examined on the merits herewith.

Claim Rejections - 35 USC § 103

Claims 1-8, 10-13, 22 and 23 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Wöber et al. (US 6,124,110) in view of Hawkins et al. (US 5,625,036), Lawson et al. ("The evaluation of complex-dependent alterations in human Factor VIIa*," J Biol Chem 267(7):4834-4843, 1992), Váradi et al. ("Monitoring the bioavailability of FEIBA with a thrombin generation assay," J Thrombosis and Heamostasis 1:2374-2380, 2003), Chan (US 5,952,198), Hogan et al. (US 6,074,826), Weinstein et al. (US 6,576,422) and Dubrow et al. (US 6,756,019), and further in view of Dou et al. (US 2002/0151582) and CRC (CRC Handbook of Chemistry and Physics 51st Ed., R.C. Weast, ed., The Chemical Rubber Co., Cleveland, 1970, p. B-77). This rejection has been discussed in the previous Office actions.

Applicants assert that the claimed invention is not obvious, because Applicants have an unexpected result. This result is that lyophilizing a mixture comprising a fluorescently labeled thrombin substrate and calcium chloride together significantly improves the solubility of the substrate in aqueous solution relative to lyophilizing these two components separately, or lyophilizing the substrate without the calcium chloride, for subsequent dissolution in a calcium chloride solution. Applicants have presented results from an experiment showing that when a solution of the fluorescently labeled thrombin substrate, in DMSO and water, is lyophilized, and,

when resolubilization in a calcium chloride solution is attempted, the substrate is difficult to dissolve, and constant stirring is required (samples 1 and 2). But, when a solution of the substrate and calcium chloride in DMSO and water is lyophilized, the substrate can be easily redissolved by adding water or a buffer (samples 3 and 4).

In reply, Applicants arguments' and Applicants' data are not commensurate in scope with the claims. The claims are very broad and recite a kit, the second component of which is a lyophilized mixture comprising any amount of any thrombin substrate that is fluorescently labeled and any amount of calcium chloride, with the functional limitation that this mixture may be dissolved in any amount of water. The comprising language does not exclude additional compounds or components from the lyophilized mixtures, such as DMSO. It is not clear from the claims or the experimental data whether or not the DMSO remains during lyophilization, as it is a solvent with a high boiling point (189 °C), or whether the DMSO evaporates during lyophilization. But, because the substrate is insoluble in water, at least enough of the DMSO remains to dissolve the substrate, or a portion of the substrate.

Applicants' data are not persuasive of unexpected results, because data for only four samples are presented. Applicants tested only one synthetic thrombin substrate (fluorescently labeled, the polypeptide Z-GGR-AMC) and one amount/concentration of calcium chloride. For the substrate that was tested, Applicants used three different amounts. But, they did not compare pairs of samples that are the same with respect to the substrate, i.e., the same amount of substrate lyophilized with and without calcium chloride. Instead, Applicants compared samples of 5 mM substrate, 10% DMSO and 2.5 mM substrate, 5% DMSO, lyophilized without calcium chloride, to 1 mM substrate, 2% DMSO, lyophilized with 15 mM calcium chloride. Presumably, the concentrations refer to those in the final solutions. The substrate solutions in DMSO and water, before lyophilization, appear to be close to the solubility limit for the

substrate. Thus, the contents of samples 1 and 2 may be less soluble than the contents of samples 3 and 4 simply because more substrate is present, in amounts that exceed the solubility limit. As a result, conclusions cannot be drawn from these data, particularly conclusions related to unexpected results.

To demonstrate this type of unexpected results, that lyophilization of the substrate with calcium chloride improves its solubility in a mixture of DMSO and water, the proper paired and controlled comparisons need to be made, a variety of fluorescently labeled thrombin substrates needs to be tested, for each substrate, a range of amounts needs to be tested, and a range of calcium chloride amounts needs to be tested. These data are critical, because of the breath of the claims.

Regarding amended claim 1, the claim now recites that water is added to form a solution, instead of an aqueous solution. But, Applicants have pointed out that the substrate, Z-GGR-AMC, is insoluble in water and that DMSO is required for making a solution. As previously discussed, the comprising language of the claim does not exclude an organic solvent, such as DMSO. Because the claim recites a lyophilized mixture of the substrate and calcium chloride, and because the claim recites the functional limitation that a clear solution forms in water, the DMSO is present either in the lyophilized mixture or in the water. As previously discussed, the prior art teaches dissolving the substrate in an aqueous solution of 10% DMSO. Thus, the amendment to the claim does not overcome the rejection.

Regarding new claim 24, as previously discussed, in the assay reaction mixtures of Váradi et al., for each test sample, 10 µl of tissue factor/phospholipid reagent is added to 50 µl of a solution of 1 mM Z-GGR-AMC and 15 mM calcium chloride. 40 µl of plasma is added to this mixture to initiate the thrombin generation reaction. The assay is carried out in microtiter plates that are read every minute for two hours at 460 nm (see p. 2375, middle of the right col.).

Thus, Váradi et al. disclose the solution recited in claim 24, which appears to be stable for at least two hours at 37 ºC, and they do not indicate that anything is insoluble in their reagent or that anything precipitates during the assay. Therefore, this claim does not distinguish Applicants' invention over the prior art.

In view of the foregoing, the rejection of record is maintained.

No claim is allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is (571)272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed, can be reached on 571-272-093434. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rosanne Kosson
Examiner, Art Unit 1652
rk/2008-11-18

/Rebecca E. Prouty/
Primary Examiner,
Art Unit 1652